UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/540,963	03/31/2000	Thomas S. Kupper	B0801/777170 (JRV)	2087

7590 02/11/2003

Wolf Greenfield & Sacks P C
600 Atlantic Avenue
Boston, MA 02210

EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/11/2003

10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/540,963	Applicant(s) Kupper
	Examiner Anne Marie Wehbé	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 26, 2002*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 5-7, 12, 13, 18-21, 25, 28-30, 36, 37, and 48* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 5-7, 12, 13, 18-21, 25, 28-30, 36, 37, and 48* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment and response received on 11/26/02 has been entered. Claims 1, 5-7, 12-14, 18-21, 25, 28-30, 36-37, and 48 are currently pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action, paper no. 7.

Claim Rejections - 35 USC § 112

The rejection of claims 1, 5-7, 12-14, 18-21, 25, 28-30, 36-37, and 48 under 35 U.S.C. 112, first paragraph rejected under 35 U.S.C. 112, first paragraph, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reason of record as discussed in detail below.

The previous office action identified the following subject matter enabled by the instant specification: 1) methods of delivering recombinant dendritic cells which express a melanoma tumor specific antigen to peripheral lymph nodes in vivo comprising further transfecting said cells with an expression vector encoding a chimeric E/L selectin polypeptide and administering said cells to a mammal wherein the expression of the chimeric E/L selectin is capable of homing the

transfected cells to peripheral lymph nodes in vivo, and 2) methods of inhibiting the growth of a melanoma in a subject comprising administering recombinant dendritic cells with express a melanoma tumor specific antigen and have been transfected with a expression vector encoding a chimeric E/L selectin polypeptide, wherein the expression of the chimeric E/L selectin is capable of homing the transfected cells to peripheral lymph nodes in vivo and inhibiting the growth of a melanoma which expresses the same melanoma specific tumor antigen expressed by the recombinant dendritic cells. The previous office action stated that the specification does not reasonably provide enablement for methods of delivering recombinant dendritic cells to any tissue in a mammal by transfecting said cell with any portion of an L, E, or P selectin, methods of delivering recombinant dendritic cells to any tissue in a mammal administering compositions comprising activated platelets and dendritic cells, or methods of vaccinating against any disease comprising administering the dendritic cells and dendritic cell compositions disclosed by the specification. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. It is further noted that the specification does not teach any purpose for directing the dendritic cells to tissues or secondary lymph nodes other than for the vaccination against disease, particularly cancer.

The applicant argues that the claims are not as broad as indicated by the examiner's use of the term "any" in reference to particular tissues and portions of selectin molecules. The applicant is reminded that the claim 1 recites methods of delivering dendritic cells to secondary lymphoid

tissue and claim 5 recites methods of delivering dendritic cells to non-lymphoid tissue. Thus, applicant's claims encompass delivery of dendritic cells to any tissue, lymphoid or otherwise, in a patient using applicant's recited method steps, i.e. administering cells to a subject. The previous office action points out that the specification fails to provide an enabling disclosure for targeting dendritic cells, or a combination of activated platelets and dendritic cells, to any type of tissue, lymphoid or otherwise, by simply administering genetically modified dendritic cells which express an "endothelial ligand binding" portion of L-selectin, E-selectin, or P-selectin using any site and route of administration.

In regards to the statement in the previous office action that the specification discloses that dendritic cells are potent antigen presenting cells and speculates that homing dendritic cells to peripheral lymph nodes or sites of chronic inflammation will result in an increased therapeutic effect on various pathogenic infections and cancer, the applicant argues that statements in the specification regarding increasing antigen presentation following increased homing of dendritic cells to peripheral lymph nodes is based on the well known antigen presenting properties of dendritic cells. The previous office did not dispute that dendritic cells are potent antigen presenting cells. The previous office action stated that the specification fails to enable the targeting of dendritic cells modified to express any "endothelial ligand binding portion" of L-selectin, E-selectin, or P-selectin other than a chimeric E/L selectin polypeptide to secondary lymphoid tissue *in vivo*, and further fails to demonstrate that the homing of unprimed dendritic

cells to peripheral lymph nodes can result in any increase in any particular type of immune response.

As stated in the previous office action, the specification teaches that dendritic cells cultured in vitro fail to home to peripheral lymph nodes and theorizes that the inability of dendritic cells to accumulate in peripheral lymph nodes is due to the low level of L-selectin on the dendritic cells. The specification further teaches that L-selectin is the main selectin responsible for lymphocyte homing to peripheral lymph nodes in vivo via binding with peripheral node addressins (PNAds). However, the specification's working examples clearly demonstrate that the transduction of dendritic cells with an retrovirus encoding L-selectin did not result in expression of L-selectin on the dendritic cell surface (specification, page 28, lines 1-4). The specification explains that L-selectin may have been rapidly degraded from the dendritic cell surface and therefore teaches the use of an E/L-selectin chimera which contains the transmembrane and intracellular domains of L-selectin and the extracellular domain of E-selectin. The specification's working examples demonstrate that dendritic cells transduced with the E/L-selectin express the E/L-selectin chimera and are capable of tethering and rolling both in vitro and in vivo on PNAd. Therefore, based on the applicant's own data, the skilled artisan would not have predicted that dendritic cells could be transfected to express sufficient levels of L-selectin capable of directing the transfected dendritic cells to peripheral lymph nodes or any other tissues in vivo.

In response, the applicant argues that the specification teaches a non-cleavable form of L-selectin on page 7. While the specification references a publication which teaches a non-cleavable

form of L-selectin, the specification does not provide any evidence that dendritic cells can be modified to express a non-cleavable form of L-selectin or that expression of such a modified L-selectin would be capable of mediating dendritic cell homing to peripheral lymph nodes *in vivo*. The applicant's working example, as discussed above, utilizes a chimeric E/L selectin wherein the endothelial binding portion is derived from E selectin. Aside from this single working example , the applicant's data does not demonstrate or suggest that wild type L, E, or P-selectin can be used to effectively target dendritic cells to lymphoid or non-lymphoid tissue in vivo, or that any chimeric or mutated L, E, or P-selectin other than the chimeric E/L selectin is capable of targeting dendritic cells to peripheral lymph nodes *in vivo*.

The applicant also argues that the data provided using the E/L chimera combined with the knowledge in the art is sufficient enablement for the use of any selectin molecule in applicant's invention. Based on applicant's own data, clearly wild type L-selectin does not work. Further, L, E, and P selectins are not functionally identical such that success using one selectin molecule would necessarily predict success using a different selectin molecule or portion of a selectin. As noted in the previous office action, E-selectin is primarily expressed by endothelial cells, whereas P-selectin is primarily expressed by platelets. Receptors for E-selectin and P-selectin are present on a number of cells which are present in many different cellular locations and are not limited to peripheral lymph nodes. P-selectin for example naturally serves as an adhesion molecule for leukocytes, not endothelial cells. While wild type E-selectin and P-selectin may have the potential to bind to elements of PNAds, the specification fails to teach the level of E-selectin or P-selectin

expression on dendritic cells sufficient to result in accumulation of dendritic cells in peripheral lymph nodes. At the time of filing, the art teaches that the process of tethering and rolling mediated by selectins is affected by the density of the selectin on the rolling cell, the identity of the selectin, the location of selectin expression on the cell surface, e.g. dispersed versus localized to the microvillus, and the density of receptors on the target cell surface (see Stein et al.). The specification fails to provide sufficient guidance for these parameters in regards to the any selectin other than the disclosed E/L-selectin. Further, as stated above, based on the expression of E-selectin and P-selectin ligands on cells located outside peripheral lymph nodes, the skilled artisan would not have predicted that the expression of any "endothelial binding portion" of E-selectin or P-selectin would in fact target transfected dendritic cells to the peripheral lymph nodes. In regards to the targeting of non-lymphoid tissue, the specification also fails to teach the level of expression of any full length or chimeric selectin capable of specifically targeting any non-lymphoid tissue. Applicant's argument that it was known in the art that receptors for selectins were expressed on non-lymphoid tissue does not meet the requirement for providing an enabling disclosure. Case law states that, " It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement" *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1005 (CAFC 1997).Thus, based on the nature or tethering and rolling mediated by selectins, the expression patterns of selectin ligands in vivo, the lack of guidance provided by the specification for the parameters affecting the targeting of specific cells to peripheral lymph nodes versus other tissues in vivo using selectin mediated adhesion, the

specification's own data demonstrating the lack of expression of L-selectin in dendritic cells transduced with L-selectin, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to practice the scope of the invention as claimed, and the skilled artisan would not have been able to predict whether the expression of any endothelial ligand binding portion of a selectin on a dendritic cell would target that cell to any particular tissue *in vivo*.

In regards to the lack of enablement for inducing any type of immune response in a mammal by administering the disclosed modified dendritic cells, the applicant argues that dendritic cells were known in the art as potent antigen presenting cells and that the vaccine claims recite wherein the composition also comprises an antigen. While claims 37 and 48 include an antigen, the method of delivery claims do not. It has been noted above and in the previous office action that the specification clearly teaches that the purpose of directing dendritic cells to peripheral lymph nodes or sites of chronic inflammation is for the vaccination or treatment of infection or disease, in particular cancer. The specification does not provide any guidance as to the amount of dendritic cells accumulating at a particular tissue in a mammal necessary to induce any type of immune response in the mammal. The specification further fails to teach the level and character of any immune response, either antigen specific or non-antigen specific, which correlates with any therapeutic effect on any pathogenic infection or disease. While the specification's working examples demonstrate the ability of dendritic cells transduced with the E/L-selectin and dendritic cell/activated platelet complexes to bind to PNAds in peripheral lymph nodes, the specification

fails to correlate the level of dendritic cell binding with the generation of any type of immune response or with the treatment or prevention of any type of pathogenic infection or disease. While dendritic pulsed with antigen or genetically modified to express a particular antigen have been demonstrated in the art to be capable of eliciting antigen specific immune responses against viral and tumor specific antigens, naive dendritic cells have not been demonstrated to be capable of generating any specific types of immune responses or to be capable of having any therapeutic effect on any disease. In order to generate a therapeutic immune response, it is necessary for naive lymphocytes to be activated by professional antigen presenting cells which present a immunogenic peptide epitope. In the absence of an immunogen, the lymphocytes are not activated. The specification provides not evidence that naive dendritic cells directed against any tissue in a mammal including the peripheral lymph nodes would be capable of activating any lymphocytes or generating any type of immune response capable of having a therapeutic effect on any disease. Based on the nature of dendritic cell induction of immune responses, which requires the presentation of immunogenic antigen, and in the absence of evidence to the contrary, the skilled artisan would not have predicted that the administration of naive dendritic cells would result in any therapeutic effect on any disease.

In regards to the unpredictability of targeting dendritic cells to particular types of tissue *in vivo,* the applicant argues that the references by the office are directed towards therapeutic gene therapy and do not specifically teach the unpredictability of targeting dendritic cells *in vivo*. The previous office action cited Deonarain, Miller, Ross, and Orkin for teaching that at the time of

filing, the targeting of vectors or cells to specific tissues or cells types in vivo, and ex vivo immunotherapy as a whole, were considered highly unpredictable. The teachings of Deonarain and Miller may not be directed particularly to the targeting of dendritic cells, however, the issues and problems identified are relevant to the instant invention. The instant invention proposes to specifically deliver cells to target tissues by modifying the cells to express a recombinant protein, a selectin molecule. Thus, the problems identified by Deonarain and Miller, i.e. expression levels of the targeting molecule, specificity of the targeting molecule, etc. are applicable to the instant invention. Furthermore, the articles by Ross and Orkin et al. have been cited to provide evidence that at the time of filing, *ex vivo* immunotherapy of disease was not considered either routine or predictable. These articles do not specifically address the instant invention, since at the time of filing, the prior art of record does not teach or suggest genetically modifying dendritic cells to express a selectin molecule in order to target either lymphoid or non-lymphoid tissue *in vivo*. Since the art is silent in regards to the predictability of using applicant's particular invention, the overall predictability of the fields of *ex vivo* immunotherapy and cell targeting *in vivo* are important in establishing the level of skill in the art. Therefore, based on the art recognized unpredictability of targeting cells in vivo to specific tissues cells, the art recognized unpredictability of treating disease using ex vivo gene therapy, the lack of guidance provided by the specification concerning the parameters affecting dendritic cell targeting to particular tissues using selectins, the lack of correlation between applicant's working examples and the generation

of any therapeutic immune response or effect on any disease, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

Finally, the applicant states that the office has not properly analyzed the specification by analyzing all eight of the factors identified in *In re Wands*. In fact, previous office action analyzed the specification in direct accordance to the factors outlined in *In re Wands*, including 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement for the instant methods. The working examples in particular were discussed in detail, as was the state of the prior art, the nature of selectins, and the predictability of the art. The applicant is also reminded that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). 35 U.S.C. 112 also requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Ultimately, ".. the disclosure of an application shall inform those skilled in the art how to use applicant's alleged

discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 6-7, 28-30, 37, and 48 under 35 U.S.C. 102(a) as being anticipated by Klein et al. is withdrawn in view of applicant's explanation and evidence that the actual publication date of the reference is December 13, 1999 and not March 13, 1999.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER